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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SEHARASEYON, JEGATHEESAN	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,732	EATON ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/17/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to comply & AppendixA* - 3

DETAILED ACTION

1. Applicant's preliminary amendment filed on 10 September 2002 is acknowledged and entered. Claims 1-20 are pending and under consideration. The claims are drawn to the nucleotide encoding protein designated PRO1573, also identified as encoded by DNA73734-1680 and ATCC accession number 203356, shown in Figures 119 (nucleic acid) and 120 (protein).

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). **Applicant is required to provide a paper copy of the CRF in response to the Office Action**.

Information Disclosure Statement

4. The information disclosure statement, filed 9/17/2002, has been considered. The BLAST results demonstrate that applicants are aware of nucleic acids with identity/homology to the one claimed herein. However, as the BLAST results do not

give sufficient identifying information, the Examiner cannot determine if said sequences constitute prior art.

Priority Determination

5. The claimed nucleotide has no utility, see rejection below. Accordingly, priority under 35 U.S.C. 120 is set at the instant filing date, 5/8/02.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to the date recited above which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession of, and fully enabled for, prior to that date.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8-10 and 14-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6a. The protein identified as PRO1573 (SEQ ID NO: 120) is not disclosed as being expressed on a cell surface. Accordingly, the limitation that the claimed protein comprises an "extracellular domain" (for example see claims 1, 6 and 14 parts (c) and (d)) is indefinite, as the art does not recognize soluble proteins as having such domains. Further, if the protein had an extracellular domain, the recitation of "the extracellular

domain", "lacking its associated signal sequence" (claim 1, 6 and 14, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell. Claims 2-5, 8-10 and 15-20 are rejected insofar as they are depended on rejected claims 1, 6 and 14.

6b. Claims that recite that the claimed polynucleotide "hybridizes to" another sequence, such as claim 14, are indefinite as there is no limiting definition of such in the specification, and the metes and bounds of that which will hybridize are dependent upon the conditions under which the hybridization is performed. As the metes and bounds of what will hybridize to a given sequence are entirely dependent upon the conditions of hybridization and washing, the metes and bounds of the claims cannot be determined. With respect to claim 15, although the further limitation that the hybridization conditions are "stringent" is introduced, the term "stringent conditions" is also a relative term, and the metes and bounds of the claim cannot be determined. Claim 15 is rejected insofar as it is depended on rejected claim 14.

Rejections under 35 U.S.C. §101 and §112

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-20 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility.

Claims 1-20 are directed to isolated polynucleotides that are 80-100% identical to (a) a sequence encoding polypeptide of SEQ ID NO: 120 or (b) a sequence encoding the polypeptide of SEQ ID NO: 120 lacking signal sequence or (c) a sequence encoding the extracellular domain of SEQ ID NO: 120 or (d) a sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 120, lacking the signal sequence or (e) a polynucleotide sequence of SEQ ID NO: 119 or (f) a full-length coding sequence of SEQ ID NO: 119 or (g) the full-length coding sequence of the cDNA deposited under ATCC 203363. Dependent claims are directed to polynucleotides that hybridize to the above sequences, vectors and host cells comprising the isolated polynucleotides. The specification discloses the isolation of a polynucleotide sequence, SEQ ID NO: 119, which encodes a protein, SEQ ID NO: 120 which is disclosed as PRO1573 (see page 21). The specification contains numerous asserted utilities the claimed nucleotides, including use as a hybridization probe, in the generation of anti-sense RNA and DNA, “knock-out” animals, as a diagnostic tool, for therapeutic purposes and for the antibody production. Further, there is no disclosure that the protein encoded by the instant nucleotides is expected to be a transmembrane protein, nor of any extracellular domain. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1573 provided in the specification. In the instant invention, claims are directed to polynucleotide sequences encoding the polypeptide of SEQ ID NO: 120 (PRO1573).

The polynucleotide (cDNA) encoding PRO1573 is disclosed to highly express in esophageal tumor, normal kidney, lung tumor and normal skin compared to normal esophagus, kidney tumor, normal lung and melanoma tumor respectively based on the microarray analysis in Example 18 (see page 144, Table 7). Table 7 also describes that many other DNA's are over expressed in various tumors and normal tissues, based on which the specification made a general assertion that an over expressed protein in a diseased tissue is useful not only as a diagnosis marker for the presence of the disease condition, but also as a therapeutic target for treatment of the disease condition. The asserted utility in diagnosis and treatment is not substantial for the following reasons. The specification does not disclose the biological significance of this high or low expression levels, nor the correlation between the high/low expression of the DNA encoding protein PRO1573 and a predisposition to the onset of lung tumor, i.e., whether it is the cause or the result of the tumors. Further, there is no supporting evidence to indicate that the polypeptide encoded by the polynucleotide of the instant invention has higher or lower expression in tumor tissues compared to their normal tissue counterparts, and as such one of skilled in the art would conclude that it is not supported by a substantial asserted utility or a well-established utility.

Although, the specification claims that the polynucleotide is more highly expressed in the esophageal tumor, normal kidney, lung tumor and normal skin the specification does not teach what is the normal level of expression, does not indicate how high the expression level is compared to for example, normal esophagus, kidney tumor, normal lung and melanoma tumor; and does not provide a statistical correlation

to the level of expression (for example, there is no indication of how many samples were compared to study the expression). Furthermore, even if the tumor is malignant, the specification fails to describe the type or kind of tumor present in esophagus, kidney, lung and skin (for example, is it an adenocarcinoma or sarcoma etc.). Without knowing the identity of the tumors, one of skill in art cannot use the polynucleotides for diagnosis or therapeutic purposes as asserted. The specification does not disclose a correlation between any specific disorder and the altered level or form of the claimed polypeptides. In addition, the specification does not teach or describe the function of this yet to be identified polypeptide. With respect to the remaining utilities, none of these asserted utilities is specific for the disclosed PRO1573 encoding polypeptides, as each of the aforementioned utilities could be asserted for any naturally occurring polypeptides, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO1573 polypeptides.

The polynucleotide may have utility because either its presence or absence or elevation or reduction is correlated to a disease. If this is not the case, then one must turn to the protein encoded by said polynucleotide to ask, "Does the protein encoded by the polynucleotide have utility?" This is a critical question because if the protein has utility, then this confers utility upon the polynucleotide from which it is transcribed or translated. However, there is no supporting evidence to indicate that the polypeptide encoded by the nucleotide of the instant invention is more highly expressed in tumor containing lung, colon and breast tissues compared to the normal lung, colon and

breast tissues. Therefore, one skilled in the art would conclude that it is not supported by a substantial asserted utility or a well-established utility.

Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12: 82-88). The data presented in the instant specification are not corrected for aneuploidy. A higher amplification of a gene does not necessarily mean higher expression or lower in a tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data of the instant invention was not supported by further analysis of mRNA or protein expression, for example. Also, the literature reports that it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression, such that the claimed polypeptides would be useful for diagnosis of cancer or as a drug target. In addition, there is no correlation between WISP-2 mRNA expression and colon tumors. This fact is documented by Pennica et al. (1998, PNAS USA 95:14717-14722). In addition, they also observed that there was no correlation between WISP-2 mRNA expression and colon tumors. Furthermore they disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the

expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." For example, WISP-2 RNA expression was significantly lower in the tumor than the mucosa (see p. 14721). Therefore, one cannot extrapolate the expression data provided in the specification to support the implicit assertion that the polynucleotide encoding PRO1573 can be used in cancer diagnosis or therapy.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleotides encoding the polypeptides. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ: at 696.

A substantial utility, by definition, is a utility the defines "real world" use, and a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use is not substantial utility. In the instant case, the higher expression of the nucleotides encoding PRO1573 in esophageal tumor, normal kidney, lung tumor and normal skin compared to tissue with normal esophagus, kidney tumor, normal lung and melanoma tumor (if significant), at the most, is an interesting invitation for further research, experimentation and confirmation as to whether the PRO1573 is useful as a diagnosis marker, or suitable as a therapeutic target for

treatment of the tumors. These further research and experimentation, however, is part of the act of invention, and until it has been undertaken, the claimed invention is not considered substantial.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8a. Claims 1-20 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above (Paragraph 6), one skilled in the art clearly would not know how to use the polynucleotide of SEQ ID NO: 119 nor polynucleotides 80, 85, 90, 95 or 99% identical to such, nor which encode a protein 80, 85, 90, 95 or 99% identical to the protein of SEQ ID NO: 120, nor polynucleotides which hybridize to any of the above.

Furthermore, even if a specific and substantial utility were subsequently established they would be enabled only for the polynucleotide of SEQ ID NO: 119 or fragments of such that are usable as hybridization probes and are not enabled for polynucleotides 80, 85, 90, 95 or 99% identical to such, nor which encode a protein 80, 85, 90, 95 or 99% identical to the protein of SEQ ID NO: 120, nor polynucleotides which hybridize to any of the above because there is n no structural or functional information provided in the specification.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re *Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are directed to isolated polynucleotides having at least 80% identity to a SEQ ID NO: 119 or that encode the protein of SEQ ID NO: 120 with or without its signal peptide, or which encode the extracellular domain of SEQ ID NO: 120 with or without its signal peptide, or polynucleotides at least 80% identical to such encoding polynucleotides. Dependent claims are directed to polynucleotides that hybridize to the above sequences, vectors and host cells comprising the isolated polynucleotides. In the instant application, there is insufficient guidance regarding how to make PRO1573 polynucleotides variants recited in the claims.

The specification also is not enabling for the breadth of claims to polynucleotide molecules that hybridize to the disclosed sequences. It is noted that claims that recite hybridization language fail to provide adequate guidance, and do not recite that the polynucleotide encodes a protein, much less one having a specifically disclosed activity. First of all, it is pointed out that the term "hybridize" or "hybridization" generically refers to a process in which a strand of polynucleotide joins or matches up with a complementary strand through the process of base pairing, wherein the process is basically used to locate or identify DNAs encoding specific proteins. It is well

established in the art that 15-20 bases have been considered sufficient to achieve this process. The breadth of the claims includes polynucleotides of as little as 10 nucleotides. With these points in mind, it is the Examiner's position that giving the claims their broadest reasonable interpretation, this language reads on an infinite number of possible DNA sequences for which there is not sufficient enablement without undue experimentation because of the breath of claims, the lack of guidance provided and the quantity of experimentation needed to make or use the invention.

With respect to the hybridization use, as discussed above in paragraph 6 the invention lacks utility and thus lacks enablement. Even if utility were established, the enablement is commensurate in scope only with claims to polynucleotides that are fragments of SEQ ID NO: 119, said fragments of sufficient length to be used as hybridization probes or primers. However, enablement is *not* commensurate in scope with fragments of polynucleotides that differ from SEQ ID NO: 119 due to codon degeneracy, as it is not recognized in the art to use such sequences that are degenerate for such detection or synthesis, and the specification provides no guidance as to how or why to make such degenerate probes or primers. The specification also is not enabling for the breadth of claims to polynucleotide molecules that hybridize to the disclosed sequences because of the quantity of experimentation needed and the lack of guidance provided by the inventor.

The examples provided in the specification do not provide working examples of different DNA sequences that would enable a representative number of the above discussed DNA sequences with assurances that they can be used as probes or primers

for the purpose of amplifying or detecting the PRO1573 gene. The mere recitation of this term, and the definitions provided do not serve as sufficient guidance to enable the breadth of the claims for the various DNA sequences claimed. See Ex parte *Forman*, 230 USPQ 546. Since the first paragraph of the statute under 35 U.S.C. 112 requires that there must be an enabling disclosure to support the breadth of the Claims, a review of the specification confirms that the scope of the various DNA sequences that are discussed above have not been enabled. There is but a single polynucleotide disclosed with reference to PRO1573, SEQ ID NO: 119. In the absence of working examples, breadth of claims and sufficient guidance, it would require undue experimentation to enable a commensurate number of the sequences that are encompassed by the claims.

Since the claimed polynucleotides are described at least in part in terms of the protein that might be encoded, the scope of the protein itself must be considered: The specification asserts that PRO1573 is an unspecified secreted and transmembrane polypeptide. However, this family of proteins does not possess a common utility, but rather the proteins that can be broadly classified and have different activities, that confer different uses on them. Accordingly, the mere identification of a protein as belonging to a family, while indicative of evolutionary relatedness, is not indicative of function, nor by extension, of utility. The structure of the putative PRO1573 peptide is briefly discussed in Figure 118, as having a putative signal sequence, corresponding to amino acids 1-23. It also describes transmembrane domain, corresponding to about amino acids 81-100, 121-141 and 173-194.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Therefore, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope, i.e. all the polynucleotides with the various percent identities.

8b. Claims 1-5 and 15-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to

be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

The claims are drawn to polynucleotides having at least 80%, 85%, 95% or 99% sequence identity with a particular disclosed sequence, or that merely hybridize to a disclosed sequence. The claims do not require that the claimed polynucleotide encode a particular protein, nor that any protein encoded thereby possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. The specification teaches that PRO1573 has (unspecified) homology to secreted and transmembrane polypeptide. The structure of the putative PRO1573 peptide is briefly discussed in Figure 118, as having a putative signal sequence, corresponding to amino acids 1-17. It also describes transmembrane domain, corresponding to about amino acids 82-101, 118-145 and 164-188. However, there is no functional characteristic associated with these motifs, hence the mere observation that they exist is not probative of function or utility. Further, there is no disclosure that the protein is expected to be a transmembrane protein, nor of any extracellular domain. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1616.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the human sequence.

Therefore, polynucleotides comprising the sequence set forth in SEQ ID NO: 119 or encoding the protein of SEQ ID NO: 120, or fragments thereof sufficiently long to be used as hybridization probes but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-*

Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless :
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9a. Claims 1-7, 9 and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Keen et al. (P56748, November 1999).

Keen et al. et al discloses nucleotides encoding the amino acid sequence of SEQ ID NO: 120 of the instant invention (Appendix A). Thus, meeting the limitations of claims 1-7, 9 and 11-13. Therefore, claims 1-7, 9 and 11-13 are rejected as being anticipated by Keen et al. (P56748, November 1999).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10a. Claims 14-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keen et al. (P56748, November 1999) in view of in view of Jacobs et al. (U.S. Patent No: 5 965 397).

The teachings of Keen et al. have been described above in paragraph 9a. However, Keen et al. does not teach hybridization of nucleic acid sequences, vector and host cells.

Jacobs et al. teaches a vector comprising the cDNA, a host cell thereof and hybridization of sequences (claims 1-4 and columns 19, 20, 24, lines: 31-65). Therefore, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to obtain vectors (with control sequences) containing DNA sequences and transfecting them into host cells as taught by Jacobs et al. by cloning the cDNA that generates a polypeptide, that is at least 100% identical to SEQ ID NO: 120 of the instant invention from DNA described by Keen et al. Similarly, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to generate nucleic acid sequences by hybridization as taught by Jacobs et al. using the polynucleotide described in Keen et al. that is identical nucleotide encoding SEQ ID NO: 120 of the instant invention. Further, Jacobs et al.

have described the expression of nucleotides containing vectors with promoter sequences in bacterial hosts (columns 23-25). With respect to the limitation of "lacking its associated signal peptide" in claims 8 and 10 as Jacobs et al. teaches recombinant expression of the said polypeptide, the cDNA would produce the polypeptide identical to the present SEQ ID NO: 120, but lacking its associated signal peptide when transfected into the host cell.

The person of ordinary skill in the art would have been motivated to clone the nucleotide sequences described by Keen et al. because it would allow for the expression of the polynucleotide and the subsequent characterization of the polypeptide. The person of ordinary skill in the art would have also been motivated to screen hybridise and obtain other nucleotide sequences that are homologous to the polypeptide described by Keen et al. because this will allow the one of skilled in the art to obtain related proteins. There is a reasonable expectation of success because transfecting the expression vector into host cell for the expression is routine in the art for expression studies and screen for new polypeptide. Therefore, the claims 14-20 are rejected as obvious over Keen et al. (P56748, November 1999) in view of in view of Jacobs et al. (U.S. Patent No: 5 965 397).

11. No claims are allowed.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JS 09/04

Brenda Brumback
BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

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Qy        181 LeuPheCysCysValPheCysCysAsnGluLysSerSerSerTyrArgTyrSerIlePro 200
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        650 CTGTTCTGCTGCGTTTTTTGTTGCAACGAAAAGAGCAGTAGCTACAGATACTCGATACCT 709

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RESULT 3
HSA250711
LOCUS       HSA250711               1931 bp    DNA     linear   PRI 11-NOV-1999
DEFINITION  Homo sapiens CLDN8 gene for claudin-8.
ACCESSION   AJ250711
VERSION     AJ250711.1  GI:6433859
KEYWORDS    claudin-8; CLDN8 gene.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Keen,T.J. and Inglehearn,C.F.
  JOURNAL   Unpublished
REFERENCE   2  (bases 1 to 1931)
  AUTHORS   Keen,T.J.
  TITLE     Direct Submission
  JOURNAL   Submitted (08-NOV-1999) Keen T.J., Molecular Medicine Unit,
            University of Leeds, Clinical Sciences Building, St James's
            Hospital, Leeds, LS9 7TF, UNITED KINGDOM
FEATURES             Location/Qualifiers
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                     /db_xref="taxon:9606"
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ORIGIN

Alignment Scores:
Pred. No.:                6.5e-123      Length:          1931
Score:                    1172.00       Matches:         225
Percent Similarity:       100.00%       Conservative:    0
Best Local Similarity:    100.00%       Mismatches:      0
Query Match:              100.00%       Indels:          0
DB:                       9             Gaps:            0

US-10-063-732-120 (1-225) x HSA250711 (1-1931)

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Db         83 ACAGTGGCTGTCACTGTCATGCCTCAGTGGAGAGTGTCGGCCTTCATTGAAAACAACATC 142

Qy         41 ValValPheGluAsnPheTrpGluGlyLeuTrpMetAsnCysValArgGlnAlaAsnIle 60
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Qy         61 ArgMetGlnCysLysIleTyrAspSerLeuLeuAlaLeuSerProAspLeuGlnAlaAla 80
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Qy        101 GlyMetLysCysThrArgCysThrGlyAspAsnGluLysValLysAlaHisIleLeuLeu 120
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Qy        121 ThrAlaGlyIleIlePheIleIleThrGlyMetValValLeuIleProValSerTrpVal 140
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Qy        161 LeuGlyGluAlaLeuTyrLeuGlyTrpThrThrAlaLeuValLeuIleValGlyGlyAla 180
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Qy        181 LeuPheCysCysValPheCysCysAsnGluLysSerSerSerTyrArgTyrSerIlePro 200
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Qy        221 ArgSerGlnTyrVal 225
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RESULT 4
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LOCUS       AX092388                2010 bp    DNA     linear   PAT 21-MAR-2001
DEFINITION  Sequence 119 from Patent WO0116318.
ACCESSION   AX092388
VERSION     AX092388.1  GI:13444508
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Eaton,D.L., Filvaroff,E., Gerritsen,M.E., Goddard,A.,
            Godowski,P.J., Grimaldi,C.J., Gurney,A.L., Watanabe,C.K. and
            Wood,W.I.
  TITLE     Secreted and transmembrane polypeptides and nucleic acids encoding
            the same
  JOURNAL   Patent: WO 0116318-A 119 08-MAR-2001;
            Genentech, Inc. (US)
FEATURES             Location/Qualifiers
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ORIGIN

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Pred. No.:                6.83e-123     Length:          2010
Score:                    1172.00       Matches:         225
Percent Similarity:       100.00%       Conservative:    0
Best Local Similarity:    100.00%       Mismatches:      0
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GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: September 1, 2004, 16:52:03 ; Search time 12 Seconds
(without alignments)
976.315 Million cell updates/sec

Title: US-10-063-732-120
Perfect score: 1172
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Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 141681 seqs, 52070155 residues

Total number of hits satisfying chosen parameters: 141681

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : SwissProt_42:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

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1	1172	100.0	225	1	CLD8_HUMAN	P56748 homo sapien
2	1012	86.3	225	1	CLD8_MOUSE	Q9z260 mus musculu
3	696	59.4	224	1	CLDH_HUMAN	P56750 homo sapien
4	534	45.6	220	1	CLD3_HUMAN	O15551 homo sapien
5	519.5	44.3	217	1	CLD9_HUMAN	O95484 homo sapien
6	516.5	44.1	210	1	CLD4_MOUSE	O35054 mus musculu
7	514	43.9	208	1	CLDY_BRARE	Q9yh91 brachydanio
8	510.5	43.6	217	1	CLD9_MOUSE	Q9z0s7 mus musculu
9	506.5	43.2	220	1	CLD6_HUMAN	P56747 homo sapien
10	506	43.2	218	1	CLD3_CANFA	Q95km5 canis famil
11	505.5	43.1	219	1	CLD3_RAT	Q63400 rattus norv
12	503.5	43.0	219	1	CLD3_MOUSE	Q9z0g9 mus musculu
13	496	42.3	209	1	CLD4_CERAE	O19005 cercopithec
14	496	42.3	219	1	CLD6_MOUSE	Q9z262 mus musculu
15	495	42.2	209	1	CLD4_HUMAN	O14493 homo sapien
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19	470	40.1	211	1	CLD7_HUMAN	O95471 homo sapien
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21	451.5	38.5	206	1	CLD5_RAT	Q9jkd6 rattus norv
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25	428	36.5	211	1	CLD1_MOUSE	O88551 mus musculu
26	417	35.6	239	1	CLDE_HUMAN	O95500 homo sapien
27	416	35.5	211	1	CLDJ_MOUSE	Q9et38 mus musculu
28	410	35.0	211	1	CLDJ_HUMAN	Q8n6f1 homo sapien
29	405	34.6	239	1	CLDE_MOUSE	Q9z0s3 mus musculu
30	399	34.0	215	1	CLDX_BRARE	Q9yh92 brachydanio
31	381.5	32.6	230	1	CLD2_MOUSE	O88552 mus musculu
32	378.5	32.3	230	1	CLD2_CANFA	Q95km6 canis famil
33	372.5	31.8	230	1	CLD2_HUMAN	P57739 homo sapien
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36	317	27.0	231	1	CLDA_MOUSE	Q9z0s6 mus musculu
37	314	26.8	219	1	CLDK_HUMAN	P56880 homo sapien
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39	308.5	26.3	220	1	CLDM_MOUSE	Q9d7u6 mus musculu
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41	297.5	25.4	227	1	CLDF_MOUSE	Q9z0s5 mus musculu
42	289.5	24.7	211	1	CLDD_MOUSE	Q9z0s4 mus musculu
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45	201	17.2	207	1	CLDB_MOUSE	Q60771 mus musculu

ALIGNMENTS

RESULT 1
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ID CLD8_HUMAN STANDARD; PRT; 225 AA.
AC P56748;
DT 30-MAY-2000 (Rel. 39, Created)
DT 30-MAY-2000 (Rel. 39, Last sequence update)
DT 15-MAR-2004 (Rel. 43, Last annotation update)
DE Claudin-8.
GN CLDN8.
OS Homo sapiens (Human).
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX NCBI_TaxID=9606;
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RP SEQUENCE FROM N.A.
RA Keen T.J., Inglehearn C.F.;
RL Submitted (NOV-1999) to the EMBL/GenBank/DDBJ databases.
RN [2]
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RX MEDLINE=20289799; PubMed=10830953;
RA Hattori M., Fujiyama A., Taylor T.D., Watanabe H., Yada T.,
RA Park H.-S., Toyoda A., Ishii K., Totoki Y., Choi D.-K., Groner Y.,
RA Soeda E., Ohki M., Takagi T., Sakaki Y., Taudien S., Blechschmidt K.,
RA Polley A., Menzel U., Delabar J., Kumpf K., Lehmann R., Patterson D.,
RA Reichwald K., Rump A., Schillhabel M., Schudy A., Zimmermann W.,
RA Rosenthal A., Kudoh J., Shibuya K., Kawasaki K., Asakawa S.,
RA Shintani A., Sasaki T., Nagamine K., Mitsuyama S., Antonarakis S.E.,
RA Minoshima S., Shimizu N., Nordsiek G., Hornischer K., Brandt P.,
RA Scharfe M., Schoen O., Desario A., Reichelt J., Kauer G., Bloecker H.,
RA Ramser J., Beck A., Klages S., Hennig S., Riesselmann L., Dagand E.,
RA Wehrmeyer S., Borzym K., Gardiner K., Nizetic D., Francis F.,
RA Lehrach H., Reinhardt R., Yaspo M.-L.;
RT "The DNA sequence of human chromosome 21.";
RL Nature 405:311-319(2000).
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RP SEQUENCE FROM N.A.
RC TISSUE=Kidney;
RX MEDLINE=22388257; PubMed=12477932;
RA Strausberg R.L., Feingold E.A., Grouse L.H., Derge J.G.,
RA Klausner R.D., Collins F.S., Wagner L., Shenmen C.M., Schuler G.D.,
RA Altschul S.F., Zeeberg B., Buetow K.H., Schaefer C.F., Bhat N.K.,
RA Hopkins R.F., Jordan H., Moore T., Max S.I., Wang J., Hsieh F.,
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RA Stapleton M., Soares M.B., Bonaldo M.F., Casavant T.L., Scheetz T.E.,
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RA Villalon D.K., Muzny D.M., Sodergren E.J., Lu X., Gibbs R.A.,
RA Fahey J., Helton E., Ketteman M., Madan A., Rodrigues S., Sanchez A.,
RA Whiting M., Madan A., Young A.C., Shevchenko Y., Bouffard G.G.,
RA Blakesley R.W., Touchman J.W., Green E.D., Dickson M.C.,
RA Rodriguez A.C., Grimwood J., Schmutz J., Myers R.M.,
RA Butterfield Y.S.N., Krzywinski M.I., Skalska U., Smailus D.E.,
RA Schnerch A., Schein J.E., Jones S.J.M., Marra M.A.;
RT "Generation and initial analysis of more than 15,000 full-length

Applicant's copy

Appendix #2

```
RT   human and mouse cDNA sequences.";
RL   Proc. Natl. Acad. Sci. U.S.A. 99:16899-16903(2002).
CC   -!- FUNCTION: Component of tight junction (TJ) strands.
CC   -!- SUBCELLULAR LOCATION: Integral membrane protein.
CC   -!- SIMILARITY: Belongs to the claudin family.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
CC   the European Bioinformatics Institute. There are no restrictions on its
CC   use by non-profit institutions as long as its content is in no way
CC   modified and this statement is not removed. Usage by and for commercial
CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
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DR   EMBL; BC058004; AAH58004.1; -.
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DR   InterPro; IPR006188; Claudin_reg.
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DR   Pfam; PF00822; PMP22_Claudin; 1.
DR   PRINTS; PR01077; CLAUDIN.
DR   PROSITE; PS01346; CLAUDIN; 1.
KW   Tight junction; Transmembrane.
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FT   TRANSMEM     82    102       POTENTIAL.
FT   TRANSMEM    118    138       POTENTIAL.
FT   TRANSMEM    167    187       POTENTIAL.
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RESULT 2
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ID   CLD8_MOUSE     STANDARD;      PRT;   225 AA.
AC   Q9Z260;
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DT   30-MAY-2000 (Rel. 39, Last sequence update)
DT   10-OCT-2003 (Rel. 42, Last annotation update)
DE   Claudin-8.
GN   CLDN8.
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OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
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RA   Morita K., Furuse M., Fujimoto K., Tsukita S.;
RT   "Claudin multigene family encoding four-transmembrane domain protein
RT   components of tight junction strands.";
RL   Proc. Natl. Acad. Sci. U.S.A. 96:511-516(1999).

RN   [2]
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RC   TISSUE=Breast tumor;
RX   MEDLINE=22388257; PubMed=12477932;
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RA   Altschul S.F., Zeeberg B., Buetow K.H., Schaefer C.F., Bhat N.K.,
RA   Hopkins R.F., Jordan H., Moore T., Max S.I., Wang J., Hsieh F.,
RA   Diatchenko L., Marusina K., Farmer A.A., Rubin G.M., Hong L.,
RA   Stapleton M., Soares M.B., Bonaldo M.F., Casavant T.L., Scheetz T.E.,
RA   Brownstein M.J., Usdin T.B., Toshiyuki S., Carninci P., Prange C.,
RA   Raha S.S., Loquellano N.A., Peters G.J., Abramson R.D., Mullahy S.J.,
RA   Bosak S.A., McEwan P.J., McKernan K.J., Malek J.A., Gunaratne P.H.,
RA   Richards S., Worley K.C., Hale S., Garcia A.M., Gay L.J., Hulyk S.W.,
RA   Villalon D.K., Muzny D.M., Sodergren E.J., Lu X., Gibbs R.A.,
RA   Fahey J., Helton E., Ketteman M., Madan A., Rodrigues S., Sanchez A.,
RA   Whiting M., Madan A., Young A.C., Shevchenko Y., Bouffard G.G.,
RA   Blakesley R.W., Touchman J.W., Green E.D., Dickson M.C.,
RA   Rodriguez A.C., Grimwood J., Schmutz J., Myers R.M.,
RA   Butterfield Y.S.N., Krzywinski M.I., Skalska U., Smailus D.E.,
RA   Schnerch A., Schein J.E., Jones S.J.M., Marra M.A.;
RT   "Generation and initial analysis of more than 15,000 full-length
RT   human and mouse cDNA sequences.";
RL   Proc. Natl. Acad. Sci. U.S.A. 99:16899-16903(2002).
CC   -!- FUNCTION: Component of tight junction (TJ) strands.
CC   -!- SUBCELLULAR LOCATION: Integral membrane protein.
CC   -!- SIMILARITY: Belongs to the claudin family.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
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CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; AF087826; AAD09761.1; -.
DR   EMBL; BC003868; AAH03868.1; -.
DR   MGD; MGI:1859286; Cldn8.
DR   InterPro; IPR006187; Claudin.
DR   InterPro; IPR006188; Claudin_reg.
DR   InterPro; IPR004031; PMP22_Claudin.
DR   Pfam; PF00822; PMP22_Claudin; 1.
DR   PRINTS; PR01077; CLAUDIN.
DR   PROSITE; PS01346; CLAUDIN; 1.
KW   Tight junction; Transmembrane.
FT   TRANSMEM      8     28       POTENTIAL.
FT   TRANSMEM     82    102       POTENTIAL.
FT   TRANSMEM    118    138       POTENTIAL.
FT   TRANSMEM    167    187       POTENTIAL.
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  Query Match             86.3%;  Score 1012;  DB 1;  Length 225;
  Best Local Similarity   82.7%;  Pred. No. 1.9e-84;
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Qy          1 MATHALEIAGLFLGGVGMVGTVAVTVMPQWRVSAFIENNIVVFENFWEGLWMNCVRQANI 60
              |||:||::| | |||||||||||||:||||||||||:||||||| ||||||||:| |||
Db          1 MATYALQMAALVLGGVGMVGTVAVTIMPQWRVSAFIESNIVVFENRWEGLWMNCMRHANI 60

Qy         61 RMQCKIYDSLLALSPDLQAARGLMCAASVMSFLAFMMAILGMKCTRCTGDNEKVKAHILL 120
              |||||:|||||||||||||:|||||||::|||||  |||||||||||||:| ||:  |||
Db         61 RMQCKVYDSLLALSPDLQASRGLMCAASVLAFLAFMTAILGMKCTRCTGDDENVKSRILL 120

Qy        121 TAGIIFIITGMVVLIPVSWVANAIIRDFYNSIVNVAQKRELGEALYLGWTTALVLIVGGA 180
              |||||| |||:||||||||||:||||||| :|:|| |||||||||:|||||||| |||
Db        121 TAGIIFFITGLVVLIPVSWVANSIIRDFYNPLVDVALKRELGEALYIGWTTALVLIAGGA 180

Qy        181 LFCCVFCCNEKSSSYRYSIPSHRTTQKSYHTGKKSPSVYSRSQYV 225
              |||||||| |:|:|||||:|||||||:|:|  |:|||:||:|||||
Db        181 LFCCVFCCTERSNSYRYSVPSHRTTQRSFHAEKRSPSIYSKSQYV 225
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Notice to Comply	Application No. 10/063 732	Applicant(s) Eaton et al.
	Examiner J. Senoraseyon	Art Unit 1647

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☑ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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